Eur J Pediatr (2007) 166:991–996
DOI 10.1007/s00431-007-0513-0

REVIEW

What is new in ventilation strategies for the neonate?

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Received: 13 March 2007 / Accepted: 8 May 2007 / Published online: 2 June 2007

Abstract A large number of ventilation strategies are now available for the neonate. This review has focused on new information, that is, studies published since 2000 and the implication of their results for current clinical practice. Meta-analysis of randomised trials has demonstrated that assist control and synchronous intermittent mandatory ventilation (SIMV) shortens the duration of ventilation only if started in the recovery rather than the early stage of respiratory disease. A recent randomised trial demonstrated pressure-regulated volume control ventilation may also have no advantages if started early. Weaning by SIMV with pressure support is better (reducing oxygen dependency) than SIMV alone. Meta-analysis of volume-targeted ventilation demonstrated significant reductions in the duration of ventilation and pneumothorax, but the trials were small and of different designs. Volume guarantee may provide more consistent blood gas control. The level of volume targeting appears to be crucial to the success of this technique. Meta-analysis of randomised trials of prophylactic high-frequency oscillation trials has shown a modest reduction in bronchopulmonary dysplasia. Randomised trials have failed to confirm the advantages of nasal continuous positive airway pressure (NCPAP) seen in various non-randomised studies; however, the randomised trials reported to date have been small. Inhaled nitric oxide (NO) does not improve the outcome of prematurely born infants with severe respiratory failure, but early low-dose prolonged iNO appears to have benefits that merit further testing. More randomised trials with long-term outcomes are required to identify the optimal ventilation strategy(ies) for the neonate.

Keywords Continuous positive airway pressure · High-frequency oscillation · Patient triggered ventilation · Ventilation · Prematurity

Abbreviations

A/C	Assist/control
BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
HFOV	High-frequency oscillation ventilation
HHFNC	Humidified high-flow nasal cannula
ICH	Intracranial haemorrhage
iNO	Inhaled nitric oxide
IPPV	Intermittent positive pressure ventilation
MAP	Mean airway pressure
PAV	Proportional assist ventilation
PS	Pressure support
PTV	Patient trigger ventilation
PVL	Periventricular leukomalacia
SIMV	Synchronised intermittent mandatory ventilation
SNIPPV	Synchronised nasal intermittent positive pressure ventilation
VG	Volume guarantee
VTV	Volume-targeted ventilation

Source of funding and grants: Atul Sharma is supported by the WellChild Trust.

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Introduction

A large number of ventilation strategies are now available for the neonate. The quality of evidence to support particular strategies, however, varies. This review has focused in particular on new information – that is, on the results of clinical studies published since 2000 – and discusses the implications of those results for current practice.

Patient-triggered ventilation (PTV)

PTV was reintroduced into neonatal intensive care in the 1980s, initially as assist/control (A/C, inflations triggered by every spontaneous breath that exceeded the critical trigger threshold) and synchronised intermittent mandatory ventilation (SIMV, only the preset number of inflations are triggered regardless of the infant's spontaneous respiratory rate).It was hoped that these ventilation modes would be more likely to promote synchrony between the infant and ventilator inflations and hence reduce airleaks and bronchopulmonary dysplasia (BPD). Unfortunately, meta-analysis of the randomised trials [16] demonstrated no significant differences in the rates of BPD, severe intracranial hemorrhage (ICH), air leaks and mortality rates according to ventilation mode. PTV was associated with a shorter duration of ventilation, but this was only seen in infants recovering from respiratory distress rather than in those in the acute stages. Similarly, in a recent randomised trial [9] in which infants were randomised at less than 6 h of age, pressure-regulated volume control ventilation (a synchronised, pressure limited A/C mode that sequentially varies the delivered pressure to approximate a target inspiratory tidal volume) compared to SIMV was not associated with an increased number of babies being extubated at 14 days.

Newer modes of triggered ventilation have now been introduced. During pressure support (PS), not only the initiation (as with A/C and SIMV) but also the termination of ventilator inflation is determined by the infant's spontaneous respiratory efforts. PS may have advantages when used as a weaning mode [36]. In a randomised trial of 107 infants of birthweights between 500 and 1000 gm, weaning by SIMV plus PS compared to weaning by SIMV (reduction in rate) alone resulted in infants of birthweights between 700 and 1000 gm requiring significantly fewer days on supplemental oxygen (41 vs. 58 days) [36]. During proportional assist ventilation (PAV), the applied pressure is servo-controlled throughout each spontaneous breath, and the frequency, timing and rate of lung inflation are controlled by the patient. The applied pressure increases in proportion to the tidal volume and inspiratory flow generated by the patient, which can be enhanced to reduce the work of breathing. In a randomised study involving extremely low birthweight infants with evolving BPD, in which 4-h periods of different ventilation modes were compared, gas exchange was maintained at lower mean and peak pressures on PAV compared to A/C or SIMV, but desaturations lasted longer on PAV [41]. These data [41] emphasise that backup conventional ventilation breaths must be provided during PAV to prevent apnoea-related desaturations [41]. A newly developed backup support (SPO_2-sensitive adaptive backup support) has been developed, and the use of this adaptive backup support with pulse oximetry-guided operation was shown to reduce the incidence and duration of oxygen desaturations [19].

Volume-targeted ventilation (VTV)

Many ventilator types designed for use in neonates can deliver a preset tidal volume; such systems are known as volume-targeted ventilation (VTV). There are different forms of VTV [28]. During volume controlled (VC) or volume support (VS) ventilation, the desired tidal volume is selected, and the duration of inflation depends on the time taken for the volume to be delivered, which is adjusted by changes in the inspiratory flow rate.

During volume guarantee (VG) ventilation, a preset expiratory tidal volume is selected, but the preset inspiratory time determines the duration of inflation. During volume limited ventilation, the pressure support for any inflation is aborted if the measured inspired tidal volume exceeds a preset upper limit. During volume control inflation there is a breath-by-breath servo-controlled flow, which is constant during inspiration so that the required volume is delivered over the set inspiratory time. Ventilator manufacturers have used different strategies to achieve VTV. The SLE 5000 and Bear Cub 750psv deliver targeted tidal or volume limited ventilation, the Draeger Babylog 8000 delivers VGV, the VIP BIRD and Avea deliver VC (or BS) ventilation and the Stephanie Paediatric ventilator delivers VC inspiration. In VTV, there are differences according to ventilator type in the delivered peak pressure, inflation time, airway pressure waveform and, hence, mean airway pressure [43]. In clinical studies, VG levels between 4 and 6 ml/kg have been used, but there is evidence to suggest that it is more appropriate to use the higher level. Greater lung inflammation was demonstrated when a volume of 3 rather than 5 ml/kg was used with SIPPV during the acute phase of respiratory distress syndrome (RDS) [25]. A level of 6 but not 4.5 ml/kg reduced the duration of hypoxemic episodes during SIMV in one study [34], and in another study, 6 ml/kg compared to 4 or 5 m/kg was associated with the lowest work of breathing [42].

Meta-analysis of the results of four randomised trials [28] demonstrated that VTV was associated with significant

reductions in the duration of ventilation and the rate of pneumothorax, but not death or BPD. The trials, however, were small; in total, only 178 infants were included in the meta-analysis. A further limitation was that different VTV modes were used in the four trials. In a subsequent randomised trial, infants with birthweights of 600–1500 gm supported by VC ventilation were compared to those supported by time-cycled pressure limited ventilation [45]; the former reached a predetermined success criterion earlier than the latter, with the difference reaching statistical significance only in babies with a birthweight less than 1000 gm. There were, however, no other advantages demonstrated. In another recent randomised study, VG with SIMV rather than SIMV alone was more effective in maintaining desirable carbon dioxide tensions in infants of greater than 25 weeks of gestational age, but was ineffective in more immature infants [7]. In very low birthweight (VLBW) infants with frequent hypoxaemic episodes, volume rather than pressure controlled SIMV was associated with less bradycardias, but it did not decrease the time spent at an oxygen saturation of less than 80% [20]. Evidence on whether the use of VG in combination with PS improves outcomes, particularly in terms of the effect on lung inflammation, is conflicting [10, 26]. In one study, the only advantage of using VG with PS was that less blood gas monitoring was required [31].

High-frequency oscillatory ventilation (HFOV)

During HFOV, small tidal volumes are delivered at frequencies of between 8 and 15 Hz. Certain oscillators display the volume delivered, but frequency can affect the accuracy of the displayed volume [24]. There have been at least 11 trials in which infants have been randomised to receive HFOV or standard ventilation techniques in the first 24 h after birth. Meta-analysis of their results [18] demonstrated that HFOV had no significant effect on mortality and only a modest reduction in BPD in terms of survivors at term; however, it had no statistically significant effect on short-term neurological abnormality, ICH or PVL. The three most recently reported randomised trials included in the meta-analysis yielded different results. Moriette et al. [29] reported that HFOV was associated with a trend towards an increase in severe ICH; the oscillator they employed has not been used in any of the other randomized trials. Courtney et al. [8] reported that HFOV reduced the combined outcome of BPD and death, but the randomized comparator group was supported by SIMV, which may have put them at a disadvantage as the work of breathing is increased at low SIMV rates. In the third trial [21] (United Kingdom Oscillation, UKOS trial), 799 infants below 29 weeks of gestation were randomised within 1 h of birth to HFOV or standard ventilation techniques, and no benefits or disadvantages of HFOV were noted. In addition, the follow-up assessments of the UKOS survivors also demonstrated no significant differences in lung function results at 1 year of age [47] or in respiratory or neurodevelopmental outcome at 2 years of corrected age [27]. HFOV is also used to "rescue" infants with severe respiratory failure. Mean airway pressure (MAP) is increased in the hope of optimising lung volume and hence oxygenation. An initial improvement in oxygenation in response to HFOV, however, does not guarantee a normal neurodevelopmental outcome at 2 years in very prematurely born infants [12].

Non-invasive respiratory support

Continuous positive airway pressure (CPAP) can be delivered by a headbox, facemask, nasaopharyngeal or endotracheal tube, single or binasal prongs. Nasal CPAP is considered by many as a gentler form of respiratory support, but it does have adverse effects, including nasal trauma in between 20 and 32% of all infants. It had been suggested that nasal trauma might particularly be a problem with dual prongs, but randomised studies have demonstrated no significant differences in the incidence of trauma between binasal prongs, a nasaopharyngeal tube [5], binasal prongs or facemask [51]. The only significant relationship to trauma in one series was CPAP duration [51]. Newer forms of CPAP include variable flow and bubble CPAP. Variable CPAP has been associated with better lung recruitment than continuous flow CPAP and a lower work of breathing. Lung overdistension, however, may occur in infants with mild disease if variable flow CPAP levels greater than 6 cm H_2O are used. During bubble CPAP, the pressure in the device is generated by a continuous flow of gas, with the distal end placed a set depth under water; the bubbles create pressure oscillations, which are transmitted back to the airway opening [33]. Clinical studies of bubble CPAP have yielded mixed results [30].

Early CPAP is now used in many centres in preference to early intubation and intermittent positive pressure ventilation (IPPV). Although early CPAP can be successful in very immature infants [4], it is more likely to fail in that group [1]. This was highlighted by a recent experience in Columbia [1]: whereas 95% of infants between 26 and 28 weeks were initially started on CPAP in the delivery room and 78% were successfully supported only by this technique, 69% of infants of 23–25 weeks were treated initially with CPAP, but only 31% could be maintained on it [1]. In a nonrandomised comparison, the application of CPAP in the delivery suite in one centre compared to intubation in the other centre was associated with fewer infants requiring supplementary oxygen at 40 weeks post-

menstrual age (P.A.) [48]. Randomised trials, however, have not confirmed the apparent benefits of CPAP reported in nonrandomised studies. Meta-analysis of two published randomised trials examining prophylactic CPAP commenced soon after birth demonstrated no significant differences in the use of mechanical ventilation or the incidence of BPD [46]. In addition, transient intubation for surfactant administration rather than nasal (n)CPAP was associated with fewer infants requiring mechanical ventilation and a lower concentration of supplementary oxygen [35]. Prophylactic CPAP (instituted within 30 min of birth) also appears not be more efficacious than rescue CPAP, which is applied when the inspired oxygen requirement is greater than 40%, as no significant differences with regard to the need for surfactant treatment or mechanical ventilation were seen in a randomised trial including 230 infants of gestational ages between 29 and 31 weeks [37]. It has been suggested that the use of early nCPAP may improve neurological outcome, as fewer cases of intraventricular haemorrhage (IVH) and abnormal neurodevelopment were seen at 6 months of age following the systematic application of early nCPAP; however, the comparison was made to historical controls [50]. In a national Danish cohort study [17], comparison at age 5 years of all 269 survivors with a birthweight below 1000 gm or a gestational age at birth of less than 28 weeks treated with early nCPAP revealed that these children have an intellectual development similar to that of a reference group of 76 term-born children [17].

Meta-analysis of the results of post-extubation randomised trials has demonstrated that CPAP significantly reduced the need for additional respiratory support (RR: 0.62, 0.49–0.77), but not the need for endotracheal intubation (RR: 0.93, 0.72–1.19) or supplemental oxygen requirement at 28 days (RR: 1.00, 0.81–1.24) [11]. Indeed, in a subsequently reported prospective randomised trial involving 97 infants, 24 h of CPAP post-extubation compared to extubation directly into a headbox was not associated with a significant reduction in reventilation [32].

An alternative to the use of nCPAP is humidified high-flow nasal cannula (HHFNC) devices. The use of HHFNC has increased in many centres because of its ease of use and perceived improved tolerance with minimal nasal trauma compared to nCPAP [44]. There has, however, been concern regarding its imprecise regulation, the generation of pressure that might occur at higher flows – particularly in the smallest of infants – as well as a potential for increased work of breathing compared to that experience on nCPAP. In a small randomised trial [39], however, no increased work of breathing was demonstrated in infants less than 2 kg on HHFNC (3–5 Lpm) compared to 6 cm H_2O nCPAP. There have been concerns regarding increased Gram-negative bacteraemia, specifically *R. picketti* [6], when using the Vapotherm 2001, a device delivering high flow which, consequently, was recalled [44]. A positive association between nasal cannula CPAP and late-onset Gram-negative blood infections in VLBW infants has also been reported and attributed to nasal trauma [15]. The introduction of humidified high-flow nasal cannula (HHFNC) into two tertiary centres was associated with an increase (not significant) of Gram-negative bacteraemia [44]. In a randomised trial, however, HHFNC maintained a normal mucosa better than standard HFNC, but the relative impact of the devices on infection rates remains to be tested [49].

A variety of nasal ventilation modes, including IPPV, SIMV or HFOV delivered by nasal prongs are being used, and there is suggestion of benefit. Extubation immediately after surfactant administration to SNIPPV rather than continuing on conventional ventilation was associated with a decreased need for supplementary oxygen and shorter durations of intubation, parental nutrition and hospitalisation [38]. Similarly, in another study, extubation to SNIPPV rather than CPAP was associated with a shorter duration of supplementary oxygen and a lower incidence of BPD (73 vs. 40%) [23]. Neither study [23, 38], however, was randomised. Older evidence is from anecdotal studies or trials with short-term outcomes; consequently, the true benefit (or the reverse) of these forms of support remains to be appropriately investigated.

Inhaled nitric oxide (iNO)

iNO, administered directly to the airway, is a selective pulmonary vasodilator used to treat hypoxemic respiratory failure associated with pulmonary hypertension of the newborn. Meta-analysis of the results of randomised trials has demonstrated that iNO reduces death or the need for extracorporeal membrane oxygenation (ECMO) in infants born at or near term, but the positive effect is the ECMO requirement [13]. Meta-analysis [3] of the results of seven trials in premature infants demonstrated that iNO had only short-term positive effects on oxygenation but no significant effects on mortality, BPD or ICH. In infants with severe respiratory failure, the use of iNO was associated with prolongation of intensive care and increased cost of care without clear beneficial effects [14]. In contrast, in one study [40], iNO was associated with a significant reduction in the combined outcome of death and BPD (RR: 0.76, 0.60–0.97) and in grade 3 and 4 IVH (RR: 0.51, 0.27–0.97); sub-analysis demonstrated the advantages were seen in the infants with relatively mild disease. Recently, two further positive iNO studies have been reported; the results of both suggest that prolonged therapy with iNO may be efficacious. In one of these studies [22], although there was no overall reduction in death or BPD in infants with birthweights between 1000 and 1250 g, low-dose (5 ppm)

iNO given for 21 days or until extubation reduced the incidence of BPD by 50% and was associated with a lower rate of the combined outcome of ICH, periventricular leukomalacia (PVL) and ventriculomegaly. In the second trial [2], iNO was associated with a significant increase in survival without BPD (43.9 vs. 36.8%), with the minimum treatment exposure being 24 days. The infants who received iNO were discharged sooner and received supplemental oxygen for a shorter time. Post hoc analysis demonstrated that the positive effects were seen in infants enrolled at 7–14 days but not at 15–21 days, and they were restricted to infants with less severe lung disease. There are ongoing trials to determine whether early, low-dose prolonged iNO will improve the long-term pulmonary outcome of immature infants with relatively mild initial disease.

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